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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,866	09/28/2006	Masanobu Kobayashi	18220-003US1ONR-A0403P-US	3917

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EXAMINER	
NATARAJAN, MEERA	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
02/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,866	KOBAYASHI ET AL.	
	Examiner	Art Unit	
	MEERA NATARAJAN	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,10-14,17-21,24,33,34 and 41-44* is/are pending in the application.

4a) Of the above claim(s) *2-5,8,11-14,18-21,24, 33,34 and 44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10,17 and 41-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/16/2006, 07/03/2006, 01/29/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, Claims 1, 10, 17 and 41-43 in the reply filed on 12/17/2007 is acknowledged.

2. Claims 6, 7, 9, 15, 16, 22, 23, 25-32 and 35-40 have been cancelled without prejudice by the Applicant's.

3. Claims 2-5, 8, 11-14, 18-21, 24, 33, 34 and 44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/17/2007.

4. Claims 1, 10, 17 and 41-43 are pending and will be examined on the merits.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 10, 17 and 41-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. The method claimed does not include any active (claims 1, 10, 17) or correlating steps (Claims 41-43). The method, as claimed, only recites one active step (1) using serine/threonine kinase Pim-1 or a partial peptide thereof or a salt thereof. This suggests that "using" Pim-1 is any way is a method of screening for a preventive, therapeutic, apoptosis-inducing, or anti-cancer agent.

8. Claim 1 is incomplete for omitting essential steps. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination. Clarification is required.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for a therapeutic agent for cancer, an apoptosis-inducing agent, or an anticancer agent comprising using serine/threonine kinase Pim-1 or a partial peptide or salt thereof, does not reasonably provide enablement for a method of screening for a preventative agent for cancer comprising using serine/threonine kinase Pim-1 or a partial peptide thereof or a salt thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

11. In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth

a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

12. The claim is drawn to a method of screening for a *preventative* agent for cancer, comprising using Pim-1, a serine/threonine kinase. The specification does not provide any teachings of a successful preventative cancer agent, how to determine the individuals who will develop a particular cancer, nor how to effectively prevent said particular cancer type before occurrence.

13. Predicting whether an individual is at risk for developing cancer is a very unpredictable art. Several factors play a role including, genetic makeup, environmental factors, age, diet, etc. For example Apantaku et al. (Breast cancer diagnosis and screening, American Family Physician 2000) reveals that most women with breast cancer have no identifiable risk factors. Although drawn to breast cancer it is relevant to the unpredictability in the art of identifying patients at risk for developing cancer or metastasis. The reference further teaches that women who have pre-menopausal first-degree relatives with breast cancer have a three- to four fold increased risk of developing breast cancer than women who do not. The risk factor of their having second-degree relatives with breast cancer

has not been quantified. The reference further teaches that genetic testing is controversial and raises issues about the reliability of tests and the use made of test results. A woman who tests negative for a particular mutation may still be at risk for developing breast cancer from a sporadic mutation or a preexisting unidentified mutation. False negative results are also possible. The reference then goes on to detail factors that may be involved with increased risk of breast cancer and suggests change of diet may alter personal risk factors. Although one group is identified as being at increased risk, there is no teaching of how or when to begin an intervention protocol.

14. A review of Martin et al (Journal of the National Cancer Institute, 92:1126-1135) reveals that it is hoped that identification of genetic and environmental factors that contribute to the development of breast cancer will enhance prevention effects. The reference reviews the state of the art of breast cancer genetic components of susceptibility to breast cancer from the standpoint of both human genetics and rat models (see abstract). The reference specifically states that despite numerous studies published to date, the role of modifier genes in breast cancer susceptibility remains to be elucidated. The resolution of ambiguous results will require further carefully designed studies with sufficient sample sizes to detect small effects. The reference concludes that great strides have been made in determining the disease etiology but that further investigation is necessary and that these studies will be crucial to evaluate the importance of new genes involved in breast cancer etiology so that scientists can define better therapies and cancer prevention (p. 1132, col 1) Finally, there is no teaching of

how or when to begin an intervention protocol. It is clear from the teachings of this reference that the art of identifying an individual at risk for malignant growth is a developing but as yet undeveloped art. The reference provides no guidance on how to determine which patients are at risk or when to administer treatment in order to inhibit the malignant cell growth for which the individual is at risk.

15. These references clearly point to the undeveloped nature of the art of reading cancer markers for the assessment of the probability of developing cancer and do not teach what interventions would have a reasonable expectation of success nor teach when or how those protocols should be administered.

16. Given the unpredictability of tumor prevention and treatment, given the unpredictability of identifying patients that are in need of cancer or metastasis prevention, one of skill in the art would not know how to use the invention as claimed. Thus, undue experimentation would be required to make and use the method as claimed as a screening method for a preventative cancer agent without undertaking to determine how to select for individuals who will develop a particular cancer type before the said cancer occurs in the individual.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1, 10, 17, 41 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al. (Archives of Biochemistry and Biophysics, Vol. 390, pp.9-18, 2001).

19. The claims are drawn to a method of screening for a therapeutic agent for cancer, an apoptosis inducing agent, or an anti-cancer agent, comprising the use of Pim-1 or a partial peptide or salt thereof. The method comprises contacting Pim-1 with a test substance that enhances or inhibits the kinase activity of Pim-1.

20. Wang et al. teach during phorbol myristate acetate (PMA) induced differentiation of U937 monoblastoid leukemia cells transfected with the dominant negative Pim-1 underwent rapid differentiation and accelerated apoptosis. The opposite effect was observed for wild-type Pim-1 (see Abstract and Fig. 9). During PMA-induced differentiation U937 cells transfected with dominant negative Pim-1 underwent apoptosis, whereas wild-type Pim-1 transfected cells did not. This suggests that Pim-1 inhibits apoptosis and a dominant negative Pim-1 construct would act as a therapeutic agent that induces apoptosis. Wang et al. disclose that when wild type Pim-1 kinase is overexpressed in U937 cells, the phosphatase activity of PTP-U2S would be decreased by Pim-1 phosphorylation, and therefore lead to a slower course of differentiation (see p. 16, right column, lines 5-12). This result is observed by the expression of the cell surface differentiation marker CD14 on the transfected cell (see Fig. 8). In contrast, the overexpression of the kinase-dead Pim-1 should be expected to promote the phosphatase activity of PTP-U2S because it functions as a dominant negative mutant to inhibit the kinase activity of endogenous Pim-1. Kinase

activity was also measured when the cells were contacted with PMA using an anti-Pim-1 antibody (see fig. 5). Wang et al. teach the active steps of claims 41 and 43 by contacting Pim-1 with PMA and determining whether kinase activity (i.e. phosphorylation) is affected (see Fig. 5). In addition, the data provided in Wang et al. determined that kinase dead Pim-1 can be used as an agent that can induce apoptosis and since the method claimed does not include any specific active steps it broadly reads on any method that identifies apoptosis inducers using Pim-1. Therefore the method performed by Wang et al. is inherently a method of screening for apoptosis-inducing agents using Pim-1 or a partial peptide thereof.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (Archives of Biochemistry and Biophysics, Vol. 390, pp.9-18, 2001) in view of Whitmarsh et al. (Methods in Enzymology, Vol. 332, pp.319-336, 2001).

20. The claim is drawn to a method of screening for substances that enhance or inhibit the activity of Pim1 comprising contacting a test substance with Pim1 and detecting the phosphorylation activity of Pim1 using a gene reporter assay that is activated in response to binding of a Pim1 phosphorylation substrate.

21. The teachings of Wang et al. have been presented in the 102(b) rejection set forth above. Wang et al. does not teach detecting phosphorylation using a reporter gene assay. This deficiency is made up for by Whitmarsh et al.

22. Whitmarsh et al. teach analyzing JNK and p38 mitogen-activated protein kinase activity. Whitmarsh et al. disclose several protocols for measuring activation state and protein kinase activity that are well known in the art. Whitmarsh et al. disclose the use of a reporter gene assay for assessing JNK and p38 activity in cells on p. 24. The method recited is a generic method well known in the art to determine activation (ie. phosphorylation). Whitmarsh discloses "the phosphorylation of the fusion protein by the protein kinase leads to increased transcription of the luciferase gene and the resulting luciferase protein can be assayed enzymatically with a luminescent substrate"

23. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the reporter gene assay taught by Whitmarsh et al. to determine phosphorylation activity of Pim-1 in the method

taught by Wang et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Whitmarsh et al. and Wang et al. because reporter gene assays help to target specific activators.

Conclusion

24. Claims 1, 10, 17 and 41-43 are rejected.

25. No claim is allowed.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MEERA NATARAJAN whose telephone number is (571)270-3058. The examiner can normally be reached on Monday-Thursday, 9:30AM-7:00PM, ALT. Friday. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO

Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MN
/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643